

The Effect of Clopidogrel Added to Aspirin in Middle-Aged Patients with Permanent Atrial Fibrillation

A. Study Purpose and Rationale

Atrial fibrillation is a common cardiac arrhythmia that increases the risk of stroke by a factor of five.¹ ATRIA, a cross-sectional study recently published in JAMA, estimates that the prevalence of atrial fibrillation to be 0.95% (increasing from .1% in those less than 55 to 9% in adults over 80). 55% of patients with atrial fibrillation are below the age of 75 and the number of patients with atrial fibrillation is predicted to increase by 2.5-fold over the next 50 years.² The morbidity and mortality associated with atrial fibrillation is high; the attributable risk of stroke increasing from 1.5% for those aged 50-59 years to 23.5% for those aged 80-89 years.

Adjusted-dose vitamin K antagonists and antiplatelet agents reduce the risk of stroke by 64% and 22%, respectively. As compared with aspirin, vitamin K antagonists reduce the risk of stroke by 38% but more than double the risk of intracranial hemorrhage and increase the risk of major extracranial hemorrhage by 70%. They have a narrow therapeutic window for benefit and require regular monitoring of coagulation studies (INR).^{3,4} Several surveys in North America and Europe indicate that only about 50% of patients with atrial fibrillation, who are at increased risk for stroke, receive vitamin K antagonists.⁵ Patients are not treated with a vitamin K antagonist for many reasons, including:

- concern about drug-drug interactions
- the increased bleeding risk
- inadequate compliance with INR monitoring
- patient preference to avoid vitamin K-antagonist therapy

However, as a consequence, most of these patients are treated with aspirin alone or are not treated at all.

The benefit of combining clopidogrel with aspirin has been proven in patients with acute coronary syndromes and in many institutions has become standard of care⁶ and recently the role of clopidogrel plus aspirin for the prevention of stroke and other vascular events in patients with atrial fibrillation was studied in ACTIVE-A, a randomized, placebo-controlled clinical trial published in May 2009 in the New England Journal of Medicine.⁷ This study demonstrated a benefit in the chosen study population for the use of clopidogrel/aspirin vs. aspirin for the prevention of stroke; however, the study did not show an overall benefit. Mortality was largely unchanged between the two groups, due, in large part, to the morbidity and mortality associated with the increased bleeding risk from dual anti-platelet therapy. Through subgroup analysis; however, the study did hint at the possibility that clopidogrel/aspirin may demonstrate a benefit in younger patients and those with permanent instead of paroxysmal/persistent atrial fibrillation.

The purpose of the proposed study is to further investigate the effect of clopidogrel plus aspirin in this patient subset, hopefully demonstrating a benefit, not only in the prevention of stroke, but in overall mortality as well (which has previously not been shown with antiplatelet

or anticoagulant therapy). Biologically, this hypothesis gains support from the observation that bleeding risk increases with age and that patients with permanent atrial fibrillation demonstrate abnormalities in platelet activation that are not consistently seen in their paroxysmal and persistent fibrillation counterparts (increases in soluble P selectin, beta-thromboglobulin) which may make them better candidates for dual anti-platelet therapy.⁸ Studies have shown that the addition of clopidogrel to aspirin results in a significantly greater reduction in platelet aggregation than that observed with aspirin alone, a result further supported by the findings of the ACTIVE-A trial.

B. Study Design and Statistical Analysis

- a. The proposed study will be a randomized, placebo-controlled, double-blind, multi-center clinical trial. Safety of the investigational treatments will be reviewed by The Data Safety Monitoring Board throughout the trial.
- b. Study Arms
 - i. Patients will be randomly assigned to one of two arms:
 1. ASA 100mg daily + placebo
 2. ASA 100mg daily + double-blind clopidogrel 75mg daily
- c. Randomization
Given the large sample size needed for statistical power, complete randomization will be performed at enrollment using random number generation.
- d. Primary and Secondary Outcomes:
 - i. Primary Outcome: The first occurrence of stroke, a non-CNS systemic embolism, myocardial infarction, or death from vascular event
 - ii. Secondary Outcomes: All cause mortality, stroke and other individual components of the primary outcome (non-central nervous system systemic embolism, myocardial infarction, and death from vascular causes) and the composite of the primary outcome and major hemorrhage.
- e. Statistical Analysis
 - i. Sample size: Using an estimated annual event rate of 8%, enrollment of 5306 patients will provide 80% power to detect a 25% difference between the study groups with an alpha of 0.05. This estimation of effect is validated by the ACTIVE A study which demonstrated a 30% difference with an overall event rate of 7.6% in placebo/ASA group and 7.4% in the age-adjusted (64-74) placebo/ASA group. However, as the primary outcome is event driven, enrollment and follow-up will be targeted to obtain the desired number of primary events.
 - ii. The primary outcome will be analyzed using a chi-squared test on proportions based on the intention-to-treat principle. Kaplan-Meier curves will be generated to document event-free survival.

C. Study Procedure

Patients will be recruited through referral from their primary care physician to a participating cardiologist or directly through a cardiologist participating in the trial. Informed consent will be obtained from each patient. Patients will be followed after randomization at month 1, month 3, month 6, and then every 6 months until the end of the trial. The estimated duration of the study is 4 years. Patients will be informed regarding the potential side effects of the medications and advised to report any signs of bleeding to their physicians.

D. Study Drugs⁹

- a. Clopidogrel

FDA-approved clopidogrel will be given in standard dosing of 75mg orally daily. *Mechanism of action:* an inhibitor of ADP-induced platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex.

Adverse side effects: as bleeding (gastrointestinal and intracranial), thrombotic thrombocytopenic purpura-hemolytic uremic syndrome, atrial fibrillation, heart failure, abdominal pain, dyspepsia, diarrhea, gastritis, headache, dizziness, arthralgia, rash, epistaxis, and hypercholesterolemia.

b. Aspirin

A dose of 100mg orally daily will be given throughout the trial to both arms.

Mechanism of action: inhibits prostaglandin synthesis and platelet aggregation

Adverse side effects: Dyspepsia, GI bleeding, ulceration and perforation, nausea, vomiting, transient elevations of hepatic enzymes, hepatitis, Reye's syndrome, pancreatitis. Prolongation of the prothrombin time, disseminated intravascular coagulation, coagulopathy, and thrombocytopenia. Acute anaphylaxis, angioedema, asthma, bronchospasm, laryngeal edema, urticaria.

E. Medical Device: N/A

F. Study Questionnaires: N/A

G. Study Subjects

a. Inclusion Criteria:

- i. Age: 64-74 years old
- ii. Permanent atrial fibrillation defined as atrial fibrillation lasting longer than 6 months that can no longer be corrected with anti-arrhythmic therapy.
- iii. At least one of the following risk factors for stroke:
 1. Systemic hypertension, on oral therapy
 2. History of prior stroke, TIA, or non-CNS systemic embolus
 3. Left ventricular dysfunction with left ventricular ejection fraction <45%
 4. Documented peripheral vascular disease
 5. Either documented prior myocardial infarction or DM requiring drug therapy

b. Exclusion Criteria:

- i. Requirement for oral anticoagulant therapy (including mechanical valve or history of PE)
- ii. History of intracerebral hemorrhage
- iii. Endoscopically documented peptic ulcer disease
- iv. History of major GI bleed requiring hospitalization
- v. Significant thrombocytopenia (platelet count <50)
- vi. Aortic stenosis

H. Recruitment of Subjects

Patients will be recruited by referral from their primary care physician or through their cardiologist.

I. Confidentiality of Study Data

All study data will be coded and data will be stored in a secure location that is only accessible to the study investigators

J. Potential Conflict of Interest

There are no conflicts of interest to disclose.

K. Location of the Study

This is a multi-center, international study which will be conducted at a variety of academic-affiliated and non-affiliated centers.

L. Potential Risks

Due to the nature of the study medications the most serious potential risk from this study is fatal hemorrhage or massive hemorrhage requiring hospitalization. All patients will be instructed on the clinical signs to look for including hematochezia, melena, hematuria, and/or hematemesis. Complete blood counts will be analyzed at each clinic session and followed throughout the trial.

M. Potential Benefits

Other than the hypothetical reduction in mortality and stroke, there are no immediate benefits to this study.

N. Alternative Therapies: N/A

O. Compensation to Subjects

Study drugs will be provided free of cost during the study and patients will be compensated for travel to follow-up visits.

P. Costs to Subjects

Additional costs incurred during the study, namely those associated with travel, will be reimbursed.

Q. Minors as Research Subjects

All patients will be greater than 18 years old.

R. Radiation or Radioactive Substances: N/A

¹Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke. The Framingham Study. *Stroke* 1991;22:983-8.

²Alan S. Go, MD; Elaine M. Hylek, MD,MPH et al. National Implications for Rhythm Management and Stroke Prevention: the AnTicoagulation and Risk Factors In Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285:2370-2375.

³Hart RG, Pearce LA, Miller VT, et al. Cardioembolic vs. noncardioembolic strokes in atrial fibrillation: frequency and effect of antithrombotic agents in the stroke prevention in atrial fibrillation studies. *Cerebrovasc Dis* 2000;10:39 - 43.

⁴van Walraven C, Hart RG, Singer DE, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient metaanalysis. *JAMA* 2002;288:2441 -8.

⁵Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *Ann Intern Med* 1999; 131:927-34.

⁶The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;345:494-502.

⁷The ACTIVE Writing Group of the ACTIVE Investigators. Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation. *N Engl J Med* 2009;360:2066-78.

⁸ Kamath S, Chin BS, Blann AD, Lip GY. A study of platelet activation in paroxysmal, persistent and permanent atrial fibrillation. *Blood Coagul Fibrinolysis* 2002; 13:627-36.

⁹ Micromedex Healthcare Series Online. <http://www.thomsonhc.com/home/dispatch>